INCIDENCE OF MYONECROSIS IN HAEMOTOXIC, NEUROTOXIC SNAKEBITES AND ITS CORRELATION WITH ACUTE RENAL FAILURE

Dissertation submitted for

MD Degree (Branch I) General Medicine
March 2008

The Tamilnadu Dr.M.G.R. Medical University
Chennai, Tamilnadu.

Madurai Medical College

CERTIFICATE

This is to certify that this dissertation titled "**INCIDENCE OF MYONECROSIS IN HAEMOTOXIC, NEUROTOXIC SNAKEBITES AND ITS CORRELATION WITH ACUTE RENAL FAILURE**" submitted by **Dr. I.VENKATESH** to the faculty of General Medicine, The Tamilnadu Dr. M.G.R. Medical University, Chennai in partial fulfillment of the requirement for the award of MD degree Branch I (General Medicine) is a bonafide research work carried out by him under our direct supervision and guidance.

Dr. M. MUTHIAH M.D.,
Additional Professor,
Department of Medicine,
Madurai Medical college,
Madurai.

Dr. A. AYYAPPAN M.D.,
Professor and Head,
Department of Medicine,
Madurai Medical College,
Madurai.

Place: Madurai.
Date:

DECLARATION

I, **Dr.I.VENKATESH**, solemnly declare that the dissertation titled **"INCIDENCE OF MYONECROSIS IN HAEMOTOXIC, NEUROTOXIC SNAKEBITES AND ITS CORRELATION WITH ACUTE RENAL FAILURE**" has been prepared by me.

This is submitted to the Tamil Nadu Dr. M.G.R. Medical University, Chennai, in partial fulfillment of the regulations for the award of MD Degree Branch I (General Medicine).

It was not submitted to the award of any degree/ diploma to any University either in part or in full form previously.

Place : Madurai

Date : **Dr. I.VENKATESH**

ACKNOWLEDGEMENT

At the outset, I wish to thank our Dean **Dr. V. RAJI M.D.,** for permitting me to use the facilities of Madurai Medical College and Govt. Rajaji Hospital to conduct this study.

My beloved Head of the department of Medicine, **Prof. A. AYYAPPAN M.D.** has always guided me, by example and valuable words of advice and has always given me his moral support and encouragement throughout the study and also during my postgraduate course. I owe my sincere thanks to him.

I owe my sincere thanks to my unit chief **Dr. M. MUTHIAH M.D.,** for his support and valuable suggestions.

I sincerely thank my beloved teachers, **Dr. Nalini Ganesh MD., Dr. P.Thirumalaikolundusubramaniam MD., Dr. P.Selvaraj M.D., Dr. M.Kamaraj M.D., Dr. Moses.K.Daniel M.D., Dr. S.VadivelMurugan M.D., Dr. D.D.Venkatraman M.D.,** for their valuable advice and guidance throughout my postgraduate course.

I offer my heartfelt thanks to my Assistant Professors **Dr. V.T.Premkumar M.D., Dr. M.Sooriyakumar M.D., Dr. G.S.Sivakumar M.D., Dr. D.Ganesapandian M.D., Dr. G.Gurunamasivayam M.D.,** for their constant encouragement, timely help and critical suggestions throughout the study and also for making my stay in the unit both informative and pleasurable.

My family and friends have stood by me during my times of need. Their help and support have been invaluable to this study.

My patients, who form the most integral part of the work, were always kind and cooperative. I pray for their speedy recovery and place this study as a tribute to them and to the numerous others likely affected.

Above all I thank the Lord Almighty for His kindness and benevolence.

ABBREVIATIONS

DIC – disseminated intravascular coagulation

CPK-MM – creatine phosphokinase (muscle fraction)

ARF – acute renal failure

BUN – blood urea nitrogen

ATN – acute tubular necrosis

PTH – parathyroid hormone

RVV – Russell’s viper venom

CONTENTS

INTRODUCTION

Snake bite is a preventable public health hazard in tropical and subtropical countries. India has always been a land of exotic snakes, which has a warm climate and dense vegetations.

The causes of renal failure in snake bite are hypotension, bleeding, DIC, direct nephrotoxicity of the snake venom and myoglobinuria. Rhabdomyolysis is a common cause of renal failure in sea snakes. Even though there is a high incidence of myonecrosis in haemotoxic snake bites, there are no extensive studies done on myonecrosis in haemotoxic and neurotoxic snake bites and its correlation with renal failure.

Better understanding of the problem is essential for the prevention and therapeutic measures to reduce if not eradicate the morbidity and mortality from snake bite.

REVIEW OF LITERATURE

EPIDEMIOLOGY

There are about 3500 species of snakes in the world. Of these 216 species of snakes are found in India, of which 52 species are poisonous. It is widely agreed that India contributes the largest share to the annual worldwide mortality due to snake bite. Mortality figures have ranged widely from 15000 to 40000 per year. Population based studies put an annual death rate of one in 10000 in the early 20th century and 3.1 per 100,000 in the 1950s. As snake bite is predominantly a rural problem and its reporting is very variable, estimating the magnitude of the problem is purely conjectural.

The circumstances of the bite and clinical development permit a good guide as to the species involved. Krait bites are usually nocturnal, indoor, unprovoked and painless. Cobra and viper bites are painful and accompanied by neuroparalysis and coagulopathy respectively. Bites by sea snakes occur mostly in the coastal areas and usually amongst the fishermen. Immunological methods for snake venom identification are not used in India despite having been established for several years elsewhere. Most bites are in the limb that are most used in the victim's occupation.

Cobra and krait are found all over India, the Russell's viper is more prevalent in the south and the saw scaled viper is more commonly found in the north and the west.

In India highest incidence is reported from Tamilnadu, Kerala, West Bengal, Maharashtra and Uttar Pradesh. No age group is exempted and males are more affected because of their frequent out door occupation

SCENERIO OF SNAKES

Common poisonous snakes encountered are

1. Elapidae – Cobra, krait, mamba and tiger snake.
2. Viperidae – Russell's viper, saw scaled viper, gaboon viper and puff adder.
3. Crotalidae – Rattlesnakes, pigmy rattlesnakes, pit viper and cottonmouths.
4. Hydrophidae – Sea snakes.
5. Colubridae – Boom slangs, bird snake of the African continent.

One can identify a poisonous snake by means of the following features:

A) Belly scales: Large and cover the entire breadth.

B) Head scales:

1) Small in viper
2) Large and conspicuous pit between the eye and nostril in pit viper.
3) Third labial touches the eye and nasal shield in cobra.
4) No pit and third labial does not touch the nose and eye and central row of scales on back enlarged; undersurface of the mouth has only four infralabials, the fourth being the largest (krait).

C) Fangs: hollow like hypodermic needle.

D) Tail: compressed

E) Habits: nocturnal

F) Teeth: two long fangs

ELAPIDAE

The cobra has a hood which on dorsal side bears a double or single spectacle mark, but it has sometimes an oval spot surrounded by an ellipse. The hood cannot be seen in a dead cobra, as the joints and neck become stiff. There are two black spots, and three black bands on the undersurface of the hood. There is a white band in the region where the hood touches the body region. The colour is brown or black. The king cobra has a hood, but no mark on it, and the length of king cobra is about three to four metres. The colour may be yellow, green, brown or black and has yellowish or white cross-bands in the body.

In kraits, the body is either steel blue with white cross bars or white cross spots (common kraits) or yellow body with black cross bars and a black stripe across the face (banded krait).

VIPERIDAE

Russell's viper has a flat, heavy and triangular head with a white V-shaped mark, the angle of the V pointing forwards. It has three rows of diamond shaped black or brown spots along the back, the outer two rows consisting of spots ringed with white edges. Its body is whitish with dark semilunar spots. It narrows towards its tail, which is short. It can be identified by the entire broad plates on the belly, the small scales on the head and the shield beneath the tail divided into two rows.

The saw-scaled viper is brown and has wavy white line on each flank of the back with diamond shaped areas between these two lines. It has a triangular head, the upper surface of which is covered with a white mark resembling an arrow. The tail is short and tapering. The broad belly plates with brown or dark spots, small scales on the head and entire shields beneath the tail are the distinguishing features.

SEA SNAKES

They have small eyes, prominent nostrils on the top of the head, broad ventrals, small tuberculated dorsal scales and paddle shaped flat tails. They are black, greenish-black or bluish-black with or without bands.

ANATOMY OF SNAKES

They have elongated body without any appendages. The tapering part of body has greater capacity to move and is called the tail. They have eyes with round and vertical pupils without eyelashes.

The lower jaw has a pair of bones, connected by a firm ligament in the front, and remains free without articulating the maxilla. This gives it the power to open the mouth widely.

Poisonous snakes have two teeth called fangs, which are present on the pre-maxilla. Duct of the poison gland opens at the base of the teeth one on either side of upper jaw below the orbit. Anteriorly the gland opens into a narrow venom-duct which ends in an ampulla like dilatation at the base of the fangs.

SNAKE VENOMS

According to the systems mainly affected by the snakes, the snakes are divided into

1) Neurotoxic : Cobra, King cobra, Krait
2) Haematotoxic : Russell's viper, Pit viper
3) Myotoxic : Sea snakes

It is essential to understand the pharmacological action of snake venom in order to device rational treatment for snake bite. A single snake may contain several varieties of poison. Important effects are produced in the heart, nervous system, blood vessels, blood, kidneys and the respiratory system. The conduction along the nerves and paralysis of the neuro-muscular junctions are the main effects on the nervous system.

The previous concept of classifying the snake venom as 1) Neurotoxins 2) Haemotoxins 3) Cardiotoxins and 4) Myotoxins would not hold true because of combination of toxins present in the venom. Venom are complex of peptides, polypeptides, enzymes, glycoproteins and other substances capable of producing several pharmacological actions which may also contain inorganic substances – sodium, potassium, calcium, zinc, manganese, etc. Zinc ions are essential for anti-cholinesterase activity. Calcium may play a role in activation of phospholipase A and the direct hemolytic factor. The more lethal fraction of snake venom appears to be peptides and certain non-enzymatic proteins.

ENZYMES

The snake venom has several enzymes. 26 such enzymes have been identified but no single snake venom contains all of them. Elapidae contains esterase that hydrolyse carbonomethoxy choline and also rich in acetylcholinesterase. Viper lacks these enzymes but are rich in endopeptidase, proteolytic enzymes, arginine ester hydrolase, thrombin like enzymes, collagenase, hyaluronidase and phospholipase.

PROTEOLYTIC ENZYMES

a) **Proteinase -** abundant in viper venom and cause marked tissue damage and destruction. The anticoagulant effect of several snake venoms may be attributable in part to the proteolytic disintegration of fibrinogen. The coagulant effect of venom may be due to conversion of prothrombin to thrombin, catalysed by the proteinases.

b) **Hyaluronidase A -** is present in almost all snake venom. It hydrolyses the hyaluronic acid and decrease the connective tissue viscosity and allows the penetration of another toxin into the surrounding tissues. It is related to the edema, swelling and rapid absorption of the toxin at the site of bite.

c) **Phospholipases (A and B) -** act as catalysts in the hydrolysis of lipids. Phospholipase A (Direct Lytic Factor) is responsible for the haemolytic effects of snake venom by their direct hydrolyzing effect on phospholipids of red cell membrane and indirectly by producing hemolytic agents (eg- lysolecithin) from plasma lecithin.

d) **Phospholipase B -** hydrolyse the lysophosphatides

e) **Phosphodiesterase -** found in the venom of all poisonous snakes. It attacks DNA, RNA and arabinose.

f) **Arginine ester hydrolase** - present in viper venom; coagulant in effect and release bradykinin.

g) **Collagenase** - a specific kind of proteinase that digests collagen.

POLYPEPTIDES

These are low molecular weight peoteins without enzymatic activity.

a) Cobra toxin :

They have neuromuscular blocking properties; also have cardiotoxic, haemotoxic and anticoagulant activities. Post synaptic neurotoxins are the principal lethal factor of cobra venom.

Cobra toxin leads to

- blockage of neuromuscular transmission
- blockage of axonal conduction
- membrane depolarization
- hemolysis
- cytotoxic action
- cardiac arrest

The cardiotoxin cause profound circulatory collapse with cardiac depression and peripheral collapse; hypotension and sudden death by cardiac arrest.

b) Haemorrhagins (HR-1 and HR-2) :

Two immunologically distinct non-enzymatic principles (HR-1 and HR-2) are typical components of viper venoms. In severe envenomation, the haemorrhagins play the major lethal role by causing haemorrhage into the vital organs – brain, lungs, kidneys, heart, GI tract, etc.

They cause severe vaso-constriction followed by vasodilatation of the micro-vessels and the arterioles with haemorrhages in the capillary bed. The vessels revealed endothelial gaps due to disintegration of the endothelial cells with intracellular oedema, swollen mitochondria and dilated endoplasmic reticulum, separation of the intercellular junction of the endothelial cells and focal loss of basement membrane of the vessels, leading to capillary and venous haemorrhages in the tissues.

The haemorrhagins act by directly disrupting the endothelial lining and by inhibiting platelet aggregation. This haemorrhgic principle also induces autocrine agents such as histamine, serotonin from tissues which open up the endothelial cell junction. HR-1 exhibits the highest haemorrhagic activity among the haemorrhagins.

OTHER TOXINS

-the snake venom protein can act either as procoagulants or anticoagulants.

-the snake venom can also be myotoxic causing rhabdomyolysis.

CLINICAL MANIFESTATIONS

The symptoms and signs of snake venom poisoning are dependent upon a number of factors.

1) AGE AND GENERAL HEALTH OF THE PATIENTS :

Younger patients are at a greater risk because of higher concentration of venom in relation to body volume of distribution. Children and elderly patients are alike and more likely to succumb easily because of poor general health.

2) NATURE, LOCATION, DEPTH AND NUMBER OF BITES :

Deeper the bite and more the number of bites, it is likely to be more lethal. Direct injection into a blood vessel will lead to rapid dissemination of venom and severe systemic envenomation. Bite through clothing is less dangerous than bite on a bare limb. Bite over an ulcerated area is more risky than over normal skin.

3) AMOUNT OF VENOM INJECTED :

This depends on the conditions of fangs and venom glands, amount and kind of clothing through which the fangs pass and factors that motivate the snake.

4) SPECIES OF THE SNAKE INVOLVED :

This will decide the symptomatology. If the snake can be identified, much of the signs and symptoms can be predicted and managed accordingly.

5) CONDITION OF THE VENOM GLANDS :

The size of the secretory cells and their contents in venom glands vary with the different stages of the secretory cycle. The rate of replenishment of the various venom components vary.

6) PATIENT'S SENSIVITY TO THE VENOM :

It will vary from person to person. Anaphylactic shock can occur in a person repeatedly bitten by snakes.

7) PATHOGENS PRESENT IN THE SNAKE'S MOUTH :

These are usually anaerobic and gram negative organisms. Anaerobic infection will be indicated by a foul smell.

CLINICAL FEATURES OF SNAKE BITE :

The symptoms and signs of snake bite result from fear, the venom and from treatment. Many patients anticipate a rapidly fatal outcome and the clinical picture may be dominated by physiological manifestations of anxiety or even frank hysteria. Non-envenomed patients may complain of feeling flushed, dizzy and breathless, may feel constriction in the chest, palpitations, tingling and spasm of the extremities resulting from hyperventilation.

Harmful effects may result from faulty first aids, traditional remedies, from tight tourniquets leading to congested and ischemic limbs, profuse bleeding and sensory loss from local incisions, etc.

SIGNS AND SYMPTOMS OF ELAPIDAE BITE

Elapid venoms are best known for their neurotoxicity. Local effects are minimal in krait, but with cobra bite, cellulitis and regional adenitis may occur. There will be salivation and vomiting initially. Earlier symptoms to occur before ptosis are contraction of frontalis muscle, blurred vision, paraesthesia around the mouth, hyperacusis, dizziness, vertigo, signs of autonomic disturbances such as hyperventilation, congested conjunctiva and goose flesh. Roughly after 15 minutes to 2 hours the signs will start occurring.

First detectable paralysis are ptosis and external ophthalmoplegia, because these muscles are sensitive to neuromuscular blockade. Later the palate, jaw, tongue, vocal cords, neck muscles and muscles of deglutition may become paralysed. Respiratory arrest may be precipitated by obstruction of the upper airway by the paralysed tongue. Intercostal muscles are affected before the limbs, diaphragm and superficial muscles. Loss of consciousness and generalized convulsions are usually explained by hypoxemia in patients with respiratory paralysis. Patients also suffer from headache, malaise and generalized myalgias. Intractable hypotension may occur in envenomation with Asian cobra.

SIGNS AND SYMPTOMS OF VIPERIDAE BITE

Haemorrhagic manifestations are the primary features in viper envenomation. Common clinical presentations are

1) Local: Cellulitis, blebs, blisters, gangrene, necrosis, bleeding from site, ulcer.
2) Systemic manifestations:
    - -circulatory failure
    - -regional lymphadenitis
    - -spreading cellulitis
    - -oliguria, anuria
    - -myoglobinuria
3) Haemorrhagic manifestations:
    - -hematuria
    - -gum bleeding
    - -epistaxis
    - -haemoptysis
    - -hemetemesis
    - -malena
    - -intracerebral bleeding
    - -sub arachnoid bleed
    - -sub conjunctival haemorrhage
    - -retinal haemorrhage
    - -retroperitoneal, intraperitoneal haemorrhage

Overt signs of hemolysis like hemoglobinuria or jaundice, are reported in Australian land snakes.

SIGNS AND SYMPTOMS OF SEA SNAKE BITE

There will be minimal local signs. After one or two hours, generalized pain and stiffness develop. Release of myoglobin, muscle enzymes and potassium leads to brown or pinkish discolouration of urine. Respiratory failure may occur.

PATHOGENESIS OF ACUTE RENAL FAILURE IN SNAKE BITE

The exact pathogenesis of ARF following snake bite is not well established. However, a number of factors may contribute *viz.* bleeding, hypotension, circulatory collapse, intravascular hemolysis, disseminated intravascular coagulation, myoglobinuria, microangiopathic hemolytic anemia and also direct nephrotoxicity of the venom.

HYPOTENSION

Bleeding either into tissues or externally, and loss of plasma into the bitten extremity can produce hypotension and circulatory collapse. This is caused by venom metalloproteinases that degrade basement membrane proteins surrounding the vessel wall, leading to loss of integrity. Hemorrhagic toxins have been isolated from venom of many snakes of Viperidae and Crotalidae families. Additionally, vasodilatation and

increased capillary permeability, both as a result of direct and indirect effects of venom, can aggravate the circulatory disturbances of shock. *Vipera palestinae* venom is thought to cause shock by depression of the medullary vasomotor center. *Bitis arietans* causes hypotension by a combination of myocardial depression, arteriolar vasodilation and increased vascular permeability. Irrespective of the cause, hypotension and circulatory collapse set in motion a chain of hemodynamic disturbances, which are known to culminate in ischemic ARF.

INTRAVASCULAR HEMOLYSIS

Another factor thought to have pathogenetic significance in snake-bite-induced ARF is intravascular hemolysis. Hemolysis results from the action of phospholipase A_2 which is present in almost all snake venoms, and a basic protein called "direct lytic factor", found only in elapid venoms. Phospholipase A_2 causes hemolysis by direct hydrolysis of red cell membrane phospholipids or indirectly via the production of the strongly hemolytic lysolecithin from plasma lecithin. Evidence of intravascular hemolysis in the form of anemia, jaundice, reticulocytosis, raised plasma free hemoglobin, abnormal peripheral blood smear, and hemoglobinuria is present in about 50% of patients following bites by the *Russell's viper* and *Echis carinatus.*

DISSEMINATED INTRAVASCULAR COAGULATION

The human hemostatic system is regulated via a number of critical interactions involving blood proteins, platelets, endothelial cells, and sub-endothelial structures. Snake venom proteins and peptides are known to activate or inactivate many of these

interactions. Snake venoms, particularly those from the viper and pit viper families, contain many proteins that interact with members of the coagulation cascade and the fibrinolytic pathway.

Russell's viper venom (RVV) contains a factor V-activating serine proteinase(RVV-V), which has been separated from a factor X-activating protein, also present in this venom. RVV-V cleaves a single peptide bond to convert factor V to factor V_a (the activated clotting protein). *Russell's viper* venom also contains a potent activator of human coagulation factor X; this enzyme has been well characterized and is designated as RVV-X. *Russell's viper* venom also activates factor IX by cleavage of a single peptide bond resulting in the formation of factor IX_a.

The enzymes present in snake venom can act as direct prothrombin activator and do not require calcium ions, phospholipids or factor V. It is apparent that the activation mechanism catalysed by the venom enzyme differs from the physiological mechanism of prothrombin activation. One or two peptide bonds are cleared by the venom enzyme during activation, generating a catalytically active intermediate. This intermediate is converted autocatalytically to normal thrombin.

Although thrombin has many activities, the ability of some snake venom enzymes to clot fibrinogen has resulted in these enzymes being called "thrombin-like". These are widely distributed primarily in the venom of snakes from true vipers and pit vipers.

Snake venom fibrinogen clotting enzymes have been classified into several groups based on the rates of release of fibrinopeptides A and B from fibrinogen.

One mechanism of the anticoagulant action of snake venom proteins is attributed to the activation of protein C. Activated protein C degrades factors V_a and $VIII_a$ and therefore, has anticoagulant activity. Another mechanism of anticoagulation involves inhibition of blood coagulation factors IX and X by a venom protein(s) that binds to either or both. Finally, anticoagulation is also achieved through the action of snake venom phospholipases that degrade phospholipids involved in the formation of complexes critical to the activation of the coagulation pathway.

Direct-acting fibrinolytic enzymes have also been isolated from the venom of snakes. Snake venom also contains a number of platelet active components, including those that cause platelet aggregation and those that inhibit platelet aggregation.

The final coagulation disturbance depends upon the balance among the activity of procoagulant, anticoagulant, fibrinolytic and fibrinogenolytic components of injected venom. The presence of fibrin thrombi in the renal microvasculature and in the glomerular capillaries, and the findings of microangiopathic hemolytic anemia and thrombocytopenia in patients with cortical necrosis strongly suggest that DIC plays a major pathogenetic role in snake-bite induced cortical necrosis. Snake venom initiates a chain reaction involving the coagulation, fibrinolytic, kinin and complement systems. Venom-induced alterations lead to vascular coagulation and to deposition of fibrin

thrombi in blood vessels. Intraglomerular fibrin deposition of lesser degree has been suspected as causing acute tubular necrosis via a temporary hemodynamic alteration.

DIRECT NEPHROTOXICITY

Snake venom can cause direct nephrotoxicity and the strongest evidence supporting direct nephrotoxicity is a dose-dependent decrease in inulin clearance and an increase in fractional excretion of sodium in the isolated perfused rat kidney, following *Russell's viper* envenomation.

MYOGLOBINURIA

The destruction of skeletal muscle and the release of muscle cell contents, notably myoglobin, into the circulation can cause an acute deterioration in renal function.Muscle damage from non-traumatic as well as traumatic causes can produce the syndrome of myoglobinuric acute renal failure(ARF), thus establishing rhabdomyolysis as a common cause of ARF on medical and surgical services of large hospitals.

A variety of conditions and diseases can lead to rhabdomyolysis and ARF. Although the list is lengthy ,it can be divided into eight basic categories 1) direct muscle injury,2) drugs & toxins-“snake venom”,3) genetic disorders causing decreased energy production,4) infections,5) excessive muscular activity,6) ischemia,7) electrolyte & endocrine/metabolic disturbances and 8) immunological diseases. The common denominator for all these causes is a disruption of normal skeletal muscle structure and

/or metabolism that leads to cell death and lysis with resulting release of intracellular contents into circulation.

MYOGLOBIN METABOLISM

Myoglobin is composed of a folded polypeptide portion(globin) and a prosthetic group, heme, which contains an atom of iron. The molecular weight of myoglobin is 17,800 daltons, which is approximately one-fourth that of the other major heme pigment, hemoglobin. The half-life of myoglobin in the circulation varies from 1 to 3 hours; after 6 hours, it has completely disappeared. Small quantities of myoglobin released during normal conditions are probably cleared by reticuloendothelial system. Larger quantities of myoglobin released from muscle in states of injury or disease are readily filtered at the glomerulus and thus can be cleared by renal mechanisms.

In the human circulation, myoglobin appears to be bound to an alpha-2 globulin that has a binding capacity of 23 mg/dl. Because myoglobin is only loosely bound to this alpha-2 globulin, at concentrations below 23 mg/dl, approximately 15% to 50% of the myoglobin is in an unbound state and is filtered (fractional clearance relative to inulin,0.75) and excreted in the urine. This interesting kinetic relationship between myoglobin and its binding protein probably explains why myoglobin is detected in the urine when plasma levels are less than 23 mg/dl. The effective renal threshold for myoglobin occurs when the plasma concentration exceeds 0.5 to 1.5mg/dl.

Although the presence of myoglobinemia or myoglobinuria is indicative of skeletal muscle injury, it may not be the most sensitive method to detect rhabdomyolysis. Given that myoglobin has a relatively rapid renal clearance (1 to 6 hrs), a patient with rhabdomyolysis may have a normal plasma level by the time he or she is hospitalized. In contrast , creatine kinase ,an intracellular muscle enzyme, appears to be a more sensitive plasma marker for rhabdomyolysis because of its slower clearance (serum half-life 1.5 days). Thus, at initial clinical evaluation, patients with rhabdomyolysis will have increased serum creatine kinase levels, whereas urinary myoglobin levels may or may not be detected.

PATHOPHYSIOLOGY OF MYOGLOBINURIC ACUTE RENAL FAILURE

The exact pathophysiology of pigment-induced ARF is unclear and is probably multifactorial. The proposed mechanisms by which myoglobinuria cause ARF include hypovolemia and renal ischemia, direct tubular toxicity of myoglobin, tubular obstruction from heme pigment casts and /or uric acid crystals, and glomerular fibrin deposition. As in many clinical syndromes, it is probably the interplay of these proposed mechanisms that results in ARF, rather than any one single factor.

HYPOVOLEMIA AND RENAL ISCHEMIA

During the initial phase of myoglobinuria induced ARF, there is a marked reduction in cardiac output(36%) and renal blood flow (20%) and an increase in renal vascular

resistance. The hemodynamic changes are due, in part, to the migration of plasma water into the sites of injury, with consequent severe intravascular volume contraction. The reduction in renal blood flow is associated with a redistribution of regional blood flow from the outer to the inner cortex and vasoconstriction of the afferent and efferent arterioles. The proposed mediators of this initial renal vasoconstriction include increased sympathetic nerve activity, augmented activity of the renin angiotensin system, reduced nitric oxide production, suppressed renal prostaglandin production, increased plasma vasopressin concentration, and formation of glomerular microthrombi. The renin angiotensin system is probably not a major factor in the pathogenesis of myoglobinuric ARF, and the studies evaluating the other listed mediators do not provide definitive evidence of their causal role. Thus, the exact mediators have not been established, and the renal vasoconstriction may be due to the interplay among a number of vasoconstricting/ vasodilating systems.

MYOGLOBIN NEPHROTOXICITY

Myoglobin is a direct nephrotoxin and is highly nephrotoxic in the setting of acidemia / aciduria and volume depletion. In an acidic medium (Ph<5.6) myoglobin dissociate into ferrihemate (hematin, molecular weight 670 daltons) and their respective globin moieties. After filtration by the glomerulus, myoglobin dissociates to ferrihemate and globin in the presence of an acid tubular fluid, or after exposure to the acid pH of cellular lysosomes, and it is the ferrihemate compound that is directly nephrotoxic.

Heme moiety is the nephrotoxic factor in myoglobinuric-induced ARF and the iron component of heme may be the specific culprit in causing renal injury. Iron can promote hydroxyl free radical formation by the Fenton-Haber-Weiss reaction, leading to lipid peroxidation and cell necrosis. Myoglobin can act as Fenton reagent.

The kidney may have its own system to contend with exposure to iron containing heme pigments. Normally, iron is released from heme by the rate limiting enzyme heme oxygenase, which acts by opening up the heme ring, generating iron and biliverdin. In turn, the liberated iron molecule can be taken up by ferritin, the major cellular repository for iron. The renal production of both heme oxygenase and ferritin is increased in the myoglobinuric ARF. The increase in heme oxygenase and ferritin production is proposed to be an adaptive response on the part of the kidney upon exposure to heme pigments and is a mechanism by which the kidney normally will degrade heme and sequester the potentially nephrotoxic iron

TUBULAR OBSTRUCTION

Filling of the tubular lumen by pigment casts that become inspissated and obstruct urinary blood flow with subsequent injury to tubular epithelium is one of the mechanisms proposed to explain the nephrotoxicity of the heme pigments. Hypovolemia and acidemia and the concomitant acidic concentrated urine facilitate precipitation of filtered myoglobin, leading to obstructive cast formation. In addition, it has been speculated that the increased urinary uric acid concentration observed in rhabdomyolysis may result in

uric acid precipitation in the tubules. Tubular obstruction can decrease GFR either by increasing the tubular pressure and thus decreasing the glomerular transcapillary hydraulic pressure or by inducing the release of factors (e.g., thrombaxane) that cause renal vasoconstriction, thereby reducing glomerular blood flow.

Although there is evidence that tubular obstruction may be a factor in the pathogenesis of the ARF, it is probably not the primary cause of the initial decrease in GFR in myoglobinuric – induced ARF. The presence of casts is the result , rather than the cause, of the decrease in GFR and urine flow. Instead of causing the initial decrease in renal function, casts formation may play a role in the maintenance of the renal failure once it develops.

GLOMERULAR FIBRIN DEPOSITION.

Due to the liberation of tissue factors, both rhabdomyolysis and intravascular hemolysis can initiate disseminated intravascular coagulation(DIC). Fibrin strands have been deposited in glomeruli. Myoglobin per se is not the cause of the renal damage, but rather it is the release of other muscle constituents which induces DIC and the subsequent deposition of glomerular microthrombi that is responsible for rhabdomyolysis-induced ARF.

LABORATORY FEATURES OF MYGLOBINURIC ACUTE RENAL FAILURE

URINE ANALYSIS

Examination of the urine provides the first laboratory clue to the presence of myoglobinuria. Classically, the initial urine is dark in color, usually with an acid pH; the benzidine or orthotoluidine reagent will give a positive reaction for blood(3+ to 4+), but microscopic examination of the urinary sediments fails to reveal any red blood cells(RBC's) or at best , only a few (<5 per HPF) indicating the presence of a heme pigment not contained within RBC's. But urinary myoglobin levels are not the most sensitive clinical marker for rhabdomyolysis.

SERUM POTASSIUM

The most life threatening consequence of rhabdomyolysis is the release of large amounts of intracellular potassium into the circulation. Since more than 98% of total body potassium resides within cells and skeletal muscle represents 60 to 70% of the total cellular mass, breakdown of even a small area of skeletal muscle will release a considerable potassium load. The presence of acidosis may shift potassium extracellularly and worsen the hyperkalemia. Admission serum potassium levels tend to be higher in patients who go on to develop ARF. About half of an acute potassium load is handled by renal excretion; therefore, in ARF, serious hyperkalemia can result and is usually the major indication for dialysis.

CREATINE KINASE

The relatively slower clearance of creatine kinase compared to myoglobin makes this enzyme level a more sensitive marker of muscle injury. Although no correlation has been established between the absolute level of the creatine kinase and the risk for the development of ARF, creatine kinase levels are significantly higher in the patients who develop ARF. Following serial serum creatine kinase levels is key to monitoring patients with rhabdomyolysis in as much as the concentration of creatine kinase may continue to increase after admission to hospitals, reflecting ongoing or worsening muscle necrosis. Increasing or decreasing creatine kinase concentrations provide some insight into whether the rhabdomyolysis is worsening or resolving.

ACID BASE BALANCE

The conditions that cause rhabdomyolysis involve tissue trauma and/or ischemia and predispose the patient to an augmented acid load. An elevated serum anion gap is usual in patients with rhabdomyolysis and is due to impaired renal excretion of intracellular organic acids released from damaged muscles, as well as retention of inorganic anions such as phosphate.

URIC ACID

Hyperuricemia is expected in patients with rhabdomyolysis . The increase in uric acid levels is due to the release of intracellular purines from damaged muscle cells, which are converted to uric acid in the liver.

BUN/ CREATININE RATIO

The rate of rise of serum creatinine relative to the rise in blood urea nitrogen (BUN) is often disproportionately greater in rhabdomyolysis-induced ARF compared to other causes of ARF. This phenomenon has been attributed to the release of larger quantities of creatine from damaged muscles and the subsequent conversion of the creatine to creatinine, resulting in a more rapid increase in serum creatinine concentration.

CALCIUM- PHOSPHORUS METABOLISM

The perturbations of calcium and phosphorus metabolism that are usually seen in most types of ARF appear to be exaggerated in rhabdomyolysis-induced ARF. Muscle damage leads to breakdown of intracellular phosphate compounds and release of large quantities of inorganic phosphorus into the circulation, resulting in hyperphosphatemia. This abnormality is accentuated when ARF impairs urinary phosphate excretion. Hypocalcemia also occurs early in the course of myoglobinuric ARF due to the deposition of calcium salts in the damaged muscles(dystrophic calcification).

Hypocalcemia may also be due to abnormalities of vitamin D and parathyroid hormone metabolism. Very low levels of 1,25- dihydroxycholecalciferol and high levels of parathyroid hormone have been noted during the oliguric phase of myoglobinuric-induced ARF. This may be due, in part, to the hyperphosphatemia associated with rhabdomyolysis in as much as hyperphosphatemia has been demonstrated to reduce renal

synthesis of vitamin D and stimulate the production of PTH. Regardless of mechanism, in the absence of frank tetany, hypocalcemia usually does not require treatment. In fact, correction of hypocalcemia with vigorous intravenous calcium replacement may increase both dystrophic and metastatic calcification.

Approximately 20%-30% of patients with myoglobinuric ARF will develop transient hypercalcemia, during recovery (diuretic) phase of their ATN. It may be due to augmentation of normal remobilization of the calcium deposits in the injured muscle, which occurs during the recovery phase of ARF. Alternatively, it has been proposed that as renal function improves, the combination of a decreasing serum phosphorus concentration and the ambient secondary hyperparathyroidism will stimulate the synthesis of vitamin D resulting in an “over shoot” hypercalcemia. This augmented vitamin D production may be due, in part, to release of vitamin D from damaged muscles.

URINARY SODIUM EXCRETION

In myoglobinuric-induced ARF, a low fractional excretion of sodium (< 1%) is observed. Hypovolemia and renal ischemia are important factors in the development of renal failure in myoglobinuric ARF and the increased sodium avidity may be due to the renal hypoperfusion. In addition to this mechanism , it is known that tubular obstruction may be a contributing factor for augmented sodium reabsorbtion. It is important to note that a low fractional excretion of sodium is not seen in all cases of myoglobinuric ARF.

DISSEMINATED INTRAVASCULAR COAGULATION(DIC)

DIC is commonly present in patients with rhabdomyolysis and may be due to the release of intracellular thromboplastins, that activate the clotting cascade. Moreover, the DIC may be a factor in the pathogenesis of ARF.

TREATMENT OF SNAKE BITE

Consists of first aid and specific management.

First aid :

-reassure the victim

-immobilize the limb with a splint or sling

-take the patient to nearby health centre as quickly as possible

-snake should be taken for species identification if it has been killed

-cauterisation, incision, suction by mouth should be avoided

-use of tourniquets is controversial.

Specific treatment :

In areas where immunodiagnostics and monovalent antivenom are available, efforts to identify the snake must be made energetically. However this is not the case in India as monovalent antivenom is not available. Polyvalent anti snake venom will reverse the neuro, haemo and myotoxic effects and their complications.

INDICATIONS FOR ASV :

Systemic envenomation :

1) Neurotoxicity – ptosis, ophthalmoplegia, etc

2) prolonged clotting time

3) features of DIC

4) spontaneous systemic bleeding

5) hypotension (shock)

6) generalized rhabdomyolysis

7) impaired consciousness.

Severe local envenomation :

1) extensive local swelling (involving more than half of the bitten limb)

2) rapidly evolving local swelling (extending beyond the bitten segment of limb – eg., above the ankle in bite of foot) within one hour of bite

3) bites in digits (fingers, toes) where venom is known to cause necrosis.

DOSAGE OF ASV :

FOR VIPERIDAE BITE :

Mild envenomation with local findings like puncture wounds, pain, soft tissue swelling confined to the bite site and no systemic findings and laboratory studies are normal – 20 to 50 ml of ASV.

Moderate envenomation with swelling extending beyond the site of bite, mild systemic findings (nausea, vomiting, muscle fasciculations, paraesthesia), mildly abnormal laboratory findings (prolonged clotting time, mildly abnormal platelet count or fibrinogen, or elevated fibrin split products) – 50 to 100 ml of ASV.

Severe envenomation with generally severe pain and swelling (may be minimal swelling with deep intramuscular or intravenous poisoning), more severe systemic findings (respiratory distress, hypotension/shock, evidence of bleeding) and very abnormal laboratory parameters – 150 to 200 ml of ASV.

Spontaneous systemic bleeding usually stops within 30 minutes of ASV and blood coagulability is restored within 6 hours of ASV. Doses may be repeated if symptoms persists for more than 6 hours of the first dose. It is advantageous to give repeated doses of ASV rather than a single dose.

FOR ELAPIDAE BITE :

Initial high doses of ASV is recommended – 100 to 150 ml. Neurotoxic signs will begin to improve within 30 minutes of ASV therapy. As in viper bite, doses may be repeated if symptoms persists for more than six hours of the first dose.

SUPPORTIVE THERAPY :

-ventilatory support in cases of respiratory paralysis.

-anti cholinesterase drugs (eg. Neostigmine 50-100 micrograms/kg) every 4^{th} hourly may produce rapid reversal of ptosis, glossopharyngeal palsy

-correction of blood loss and hypovolemia

-tetanus toxoid

-antibiotics to cover gram negative organisms and anaerobes

-management of acute renal failure

-fasciotomy for intracompartmental syndrome.

TREATMENT OF MYOGLOBINURIC ARF :

Because hypovolemia and renal ischemia are important factors in the pathogenesis of myoglobinuric-ARF, it has been recognized that early and vigorous intravenous fluid therapy is important in attenuating renal injury. Based on the notion that myoglobin is more nephrotoxic at an acidic pH, most groups advocate the addition of sodium bicarbonate to the i.v fluids for the purpose of alkalinization of the urine. By correcting cellular acidosis, bicarbonate therapy may reduce renal tubular epithelial swelling and attenuate renal tubular and vascular collapse. Further, this therapy may ameliorate the hyperkalemia commonly seen in rhabdomyolysis.

Mannitol has long been recognized to be an effective agent in the prophylaxis against the development of experimental and clinical ARF and has been used in combination with fluid/alkaline therapy to prevent the renal injury in patients with rhabdomyolysis. Effects of mannitol include a decrease in blood viscosity and in oncotic pressure across the glomerulus to facilitate and increase in GFR, dilatation of glomerular capillaries and stimulation of prostaglandin release, increase in urine flow and prevention of obstructing cast formation, reduction in renal tubular epithelial swelling and injury, and scavenging of oxygen free radicals. In addition, mannitol may have extrarenal benefit such as extracellular volume expansion, an increase in cardiac contractility, increased release of ANF, and reduction in skeletal muscle edema with consequent decompression of muscle tamponade.

Furosemide, a loop acting diuretic, has the theoretic advantage of inhibiting sodium transport in the thick ascending limb of Henle's loop. By inhibiting sodium transport, furosemide may reduce oxygen consumption in the face of limited delivery and thereby preserve cell viability. In addition, the augmented urinary flow induced by the diuretic may mitigate against tubular obstruction. Loop diuretics, however, have the theoretic disadvantage of increasing acidification of urine, worsening intravascular volume depletion if urinary losses are not replaced, and inducing ototoxicity; thus, the use of these agents has not been generally recommended.

Although there are no controlled trials to show a direct benefit of a forced alkaline-mannitol diuresis in the prevention of ARF in rhabdomyolysis, there are many case reports suggesting such therapy was instrumental in averting renal injury. Initially, optimization of intravascular fluid volume deficits should be carried out with dispatch using isotonic crystalloid solutions, usually normal saline. Variables useful in following this course of therapy include physical examination of the state of the circulation, serial measurement of hematocrit, and recording of external fluid balance. If the clinic assessment suggests that a euvolemic state has been achieved but no improvement in oliguria has occurred, the decision must be made about further intervention. Usually by this time, laboratory results will offer further support for the diagnosis of myoglobinuria and acute renal insufficiency and the prompt infusion of mannitol-bicarbonate solution is recommended. This is made by adding two ampoules, each containing 12.5 g of mannitol in 50 ml, and two ampoules of 50 meq of sodium bicarbonate in 50 ml to 800 ml of 5% dextrose in water for intravenous infusion. This reconstituted liter is roughly isosmotic

with plasma once the glucose is metabolized and contains both mannitol and 100 meq of sodium bicarbonate. It should be infused at 250ml/hour; urine flow rate should increase by the end of the 4 hour infusion if the treatment is successful. If this is the case, the solution should continue to be administered at a rate equal to urine output until such time as azotemia has started to clear and all evidence of myoglobinuria has disappeared. If urine fiow does not increase after the 4 hour infusion, the patient has entered the established phase of oliguric ARF and should be treated conservatively until dialysis can be arranged. When ARF has become established, hemodialysis must be done.

The prognosis for the renal failure is good, but the ultimate prognosis is more dependent on other comorbid conditions such as sepsis, bleeding and respiratory failure.

AIM OF THE STUDY

1) To study the incidence of myonecrosis in haemotoxic and neurotoxic snake bites.
2) To correlate CPK-MM levels with acute renal failure.

MATERIALS AND METHODS

Patients admitted in the medical wards of Govt. Rajaji Hospital, Madurai formed the materials of this study. Totally, 100 patients have been studied. History, clinical findings and investigations were written in printed proforma.

INCLUSION CRITERIA :

1) All patients with definite history of snake bite.
2) Patients above 12 years of age.

EXCLUSION CRITERIA :

1) Chronic kidney disease
2) Hypotension
3) Sepsis
4) Acute coronary syndromes
5) Patients who had intramuscular injection one week before the snake bite.

CPK-MM levels are detected using kinetic methods and myoglobinuria is detected using spectroscopy.

The levels of CPK-MM are graded for convenience purpose, as given in the following table.

CPK MM	SEVERITY
LESS THAN 140	(NORMAL)
140 - 499	(1+)
500 – 999	(2+)
1000 – 1499	(3+)
1500 – 1999	(4+)
2000 AND ABOVE	(5+)

STATISTICAL TOOLS :

The information collected regarding all the selected cases were recorded in a master chart. Data analysis was done with the help of computer using Epidemiological Information Package (EPI 2002).

Using this software, frequencies, percentage, mean, standard deviation and `p' values were calculated. A `p. value of less than 0.05 is taken to denote significant relationship.

RESULTS

AGE DISTRIBUTION OF SNAKE BITE CASES :

Table 1 shows the age distribution of 100 snake bite cases. The incidence of snake bite cases is more in 20-49 years of age. The mean age is 34.86

Table 1

Age Distribution of snake bite cases

Age in Years	**Cases**	
	No.	**%**
Less than 20	11	11
20-29	24	24
30-39	26	26
40-49	25	25
50-59	11	11
60 & above	3	3
Total	100	100
Mean	**34.86**	
S.D.	**12.83**	

TYPE OF SNAKE

Table 2 shows the number of patients bitten due to different types of snakes. Viper bite constitute 79%, cobra bite 4%, krait bite 3% and unknown snake bites 14%.

Table 2

Type of Snake

Type of Snake	Cases	
	No.	**%**
Viper	79	79
Cobra	4	4
Krait	3	3
Unknown	14	14
Total	100	100

INCIDENCE OF CELLULITIS DUE TO DIFFERENT TYPES OF SNAKES :

Table 3 shows the incidence of cellulitis due to different types of snakes. 91.1% of viper bite causes cellulitis and 50% of cobra bite causes cellulitis. There was no cellulitis in krait bite. This difference is statistically significant with a `p' value of 0.0007.

Table 3

Type of snake and Cellulitis

Type of snake	**Cellulitis**			
	Present		**Absent**	
	No.	**%**	**No.**	**%**
Viper(79)	72	91.1	7	8.9
Cobra (4)	2	50	2	50
Krait (3)	-	-	3	100
Unknown(14)	10	71.4	4	28.6
'p'	**0.0007** **Significant**			

CORRELATION OF CELLULITIS WITH DEGREE OF MYONECROSIS :

Table 4 shows the correlation of cellulitis with the degree of myonecrosis. Our study revealed a direct correlation between cellulitis and the degree of myonecrosis. The mean CPK-MM value in patients with cellulitis is 735.5 IU/L and the mean CPK-MM value in patients without cellulitis is 94.4 IU/L and this difference is statistically significant with a `p' value of 0.0001.

Table 4

Correlation of cellulitis with degree of myonecrosis

Cellulitis	**CPK-MM**	
	Mean	**S.D**
Present(n=84)	735.5	573.2
Absent(n=16)	94.4	14.9
p	**0.0001 (significant)**	

INCIDENCE OF MYONECROSIS IN SNAKE BITE :

Table 5 shows the incidence of myonecrosis in 100 snake bite patients. The incidence of myonecrosis in our study was 81%. The mean CPK-MM level is 632.9 IU/L and the range being 56 to 2162.

Table 5

Level of CPK-MM in 100 snake bite patients

CPK MM	**Cases**	
	No.	**%**
Less than 140 (Normal)	19	19
140-499 (1+)	35	35
500-999 (2+)	29	29
1000-1499 (3+)	6	6
1500-1999 (4+)	3	3
2000 & above (5+)	8	8
Total	100	100
Mean	**632.9**	
S.D.	**575.6**	

AGE DISTRIBUTION OF MYONECROSIS IN SNAKE BITE :

Table 6 shows the age distribution of myonecrosis in 100 snake bite patients. Out of 100 patients studied it was noted that the degree of myonecrosis was high in patients less than 40 years of age. Table 3 shows the age wise distribution of myonecrosis and the difference among the age wise distribution of myonecrosis is statistically significant with a `p' value of 0.0097

Table 6

Age distribution of myonecrosis in snake bite

Age Group	**CPK MM**	
	Mean	**S.D.**
Less than 20	1048.5	778.8
20-29	755.3	676.7
30-39	685	581.2
40-49	313	261
50-59	616.3	304.7
60 & above	406.3	275.9
'p'	**0.0097 (Significant)**	

SEX DISTRIBUTION OF MYONECROSIS IN SNAKE BITE :

Table 7 shows the sex distribution of myonecrosis in 100 snake bite patients. There was no statistically significant difference in the sex wise distribution of myonecrosis in snake bite. The mean CPK-MM value in males is 622.2 IU/L and the mean CPK-MM value in females is 660.4 IU/L and the `p' value is 0.878 (not significant)

Table 7

Sex distribution of myonecrosis in snake bite

Sex	**CPK MM**	
	Mean	**S.D.**
Males	622.2	565.3
Females	660.4	611.1
p	**0.878 (Not significant)**	

DEGREE OF MYONECROSIS IN VARIOUS TYPES OF SNAKE BITE :

Table 8 shows the degree of myonecrosis in various types of snake bite. Our study revealed that viper snake bites have a higher degree of myonecrosis with a mean CPK-MM value of 676.4 IU/L, followed by unknown snake bites with a mean CPK-MM value of 624.3 IU/L, which is followed by cobra bite with a mean CPK-MM value of 204.5 IU/L and the least in krait with a mean CPK-MM value of 100 IU/L. This difference is statistically significant with a `p' value of 0.0126

Table 8

Degree of myonecrosis in various types of snake bite

Type of Snake	**CPK MM**	
	Mean	**S.D.**
Viper	676.4	574.4
Cobra	204.5	147.5
Krait	100	6.9
Unknown	624.3	636.3
p	**0.0126** **Significant**	

CORRELATION OF THE DEGREE OF MYONECROSIS WITH MYOGLOBINURIA

Table 9 shows the correlation of the degree of myonecrosis with myoglobinuria. Our study revealed that there is a direct correlation between the degree of myonecrosis and myoglobinuria. The mean CPK-MM value in patients with myoglobinuria is 2028.4 IU/L and the mean CPK-MM value in patients without myoglobinuria is 477.9 IU/L and this difference is statistically significant with a `p' value of 0.0001

Table 9

Correlation of the degree of myonecrosis with myoglobinuria

Myoglobunuria	**CPK MM**	
	MEAN	**SD**
Present	2028.4	92.9
Absent	477.9	352.9
p	**0.0001 (Significant)**	

CORRELATION OF THE DEGREE OF MYONECROSIS WITH RENAL FAILURE :

Table 10 shows the correlation between the degree of myonecrosis and renal failure. The renal failure patients have a higher level of CPK-MM elevation. The mean CPK-MM value in patients with renal failure is 2047.8 IU/L and the mean CPK-MM value in patients without renal failure is 509.9 IU/L and this difference is statistically significant with a `p' value of 0.0001

Table 10

Correlation of the degree of myonecrosis with renal failure

Renal failure	**CPK MM**	
	MEAN	**S D**
Absent	509.9	410.6
Present	2047.8	84.4
p	**0.0001 (Significant)**	

TYPE OF SNAKE BITE AND RENAL FAILURE :

Table 11 shows the incidence of renal failure caused due to various types of snake bite. The incidence of ARF in our study is 8%. Of these 8 patients with renal failure, 6 were due to viper bite and 2 were due to unknown bite. In our study, 7.6% of viper bites have caused renal failure and 14.3% of unknown snake bites have caused renal failure.

Table 11

Type of snake bite and renal failure

Type of Snake	Cases of			
	Renal Failure		Normal	
	No.	%	No.	%
Viper (79)	6	7.6	73	92.4
Cobra (4)	-	-	4	100
Krait (3)	-	-	3	100
Unknown (14)	2	14.3	12	85.7

DISCUSSION

The age distribution of snake bite in our study shows the age group between 20-49 years constitute 75% of the snake bite cases. This is related to the outdoor activities of this age group. Older people are least involved because of sedentary habits.

In our study, cellulitis was present in 84% of patients. 91.1% of patients with viper bite developed cellulitis, 50% of patients with cobra bite developed cellulitis and there was no cellulitis in krait bite. The reason for this prevalence of cellulitis in viper bite is because the enzyme metalloproteinase and the proteolytic enzymes are more abundant in Crotalidae and Viperidae snakes. These enzymes cause more tissue destruction and damage. Proteolytic enzymes produce local changes in vascular permeability leading to oedema, blistering, bruising and necrosis. Proteolytic enzymes are present in lesser amounts in Elapidae and hence, they cause minimal cellulitis. In a study conducted by Philips et al, 73% of patients had cellulitis. In our study, the incidence of cellulitis is 84%.

Creatine kinase-MM levels correlates directly with the presence of cellulitis. CPK-MM elevation is seen only in patients with cellulitis and CPK-MM is not elevated in patients without cellulitis.

The incidence of myonecrosis in our study is 81%. A significant proportion of patients had only minimal elevation of CPK-MM (35% of patients have CPK-MM levels less than 500 IU/L). 29% of patients have CPK-MM levels between 500-999 IU/L. 6% of patients have CPK-MM levels between 1000-1499 IU/L. 3% have CPK-MM levels between 1500-1999 IU/L and 8% have CPK-MM levels greater than 2000 IU/L. The level of CPK-MM elevation is very much low when compared to the CPK-MM elevation seen in sea snake bites. The incidence of myonecrosis is higher in our study because of the more prevalence of viper in this part of our country. 79% of snake bites in our study were due to viper.

High levels of CPK-MM elevation is seen more in patients less than 40 years of age. This may be due to the degree of envenomation and there is no study done correlating the age distribution of myonecrosis.

The degree of myonecrosis is equal in males and females and there is no significant statistical difference among the sex wise distribution of myonecrosis.

CPK-MM elevation is more with viper bite when compared to cobra and krait bites. This is because of the greater amount of tissue damage caused by proteolytic enzymes in viper bite. Cobra causes minimal cellulitis and hence mild elevation of CPK-MM. There are no local effects in krait bite and therefore CPK-MM is not elevated. A significant level of CPK-MM elevation is seen in unknown snake bites. This can be explained, that most of the unknown bites may be due to viper.

Out of 100 patients, 8 patients developed renal failure. In a study conducted by Philips et al, 9% of his patients developed renal failure. In our study, all renal failure patients had myoglobinuria. In a study conducted by Philips et al, 60.86% of his had myoglobinuria. This can be explained that a different species of viper snake may be involved in his study. Neurotoxicity was the commonest sign in his study and 82% had external ophthalmoplegia and 77% had ptosis. But, neurotoxicity was not reported in viper bites in our study. This explains that a different species of viper snake may be involved in his study.

Myoglobinuria correlates directly with the level of CPK-MM elevation. The patients who developed renal failure have greater elevation of CPK-MM. Seven patients have levels greater than 2000 IU/L and one patient has a value of 1874 IU/L. This shows that there is a definite correlation between the level of CPK-MM elevation and renal failure. The mechanism by which rhabdomyolysis causes renal failure are hypovolemia, renal ischemia, direct nephrotoxicity of myoglobin, tubular obstruction from heme pigment casts/ uric acid crystals and DIC.

Although the presence of myoglobinemia or myoglobinuria is indicative of skeletal muscle injury, it may not be the most sensitive method to detect rhabdomyolysis. As myoglobin has a relatively rapid renal clearance(1-6 hours), a patient with rhabdomyolysis may have a normal plasma level by the time he or she is hospitalized. In contrast, creatine kinase, appears to be a more sensitive plasma marker for rhabdomyolysis because of its slower clearance(serum half-life 1.5 days). Thus, at initial

clinical evaluation, patients with rhabdomyolysis will have increased serum creatine kinase levels, whereas urine myoglobin levels may or may not be detected.

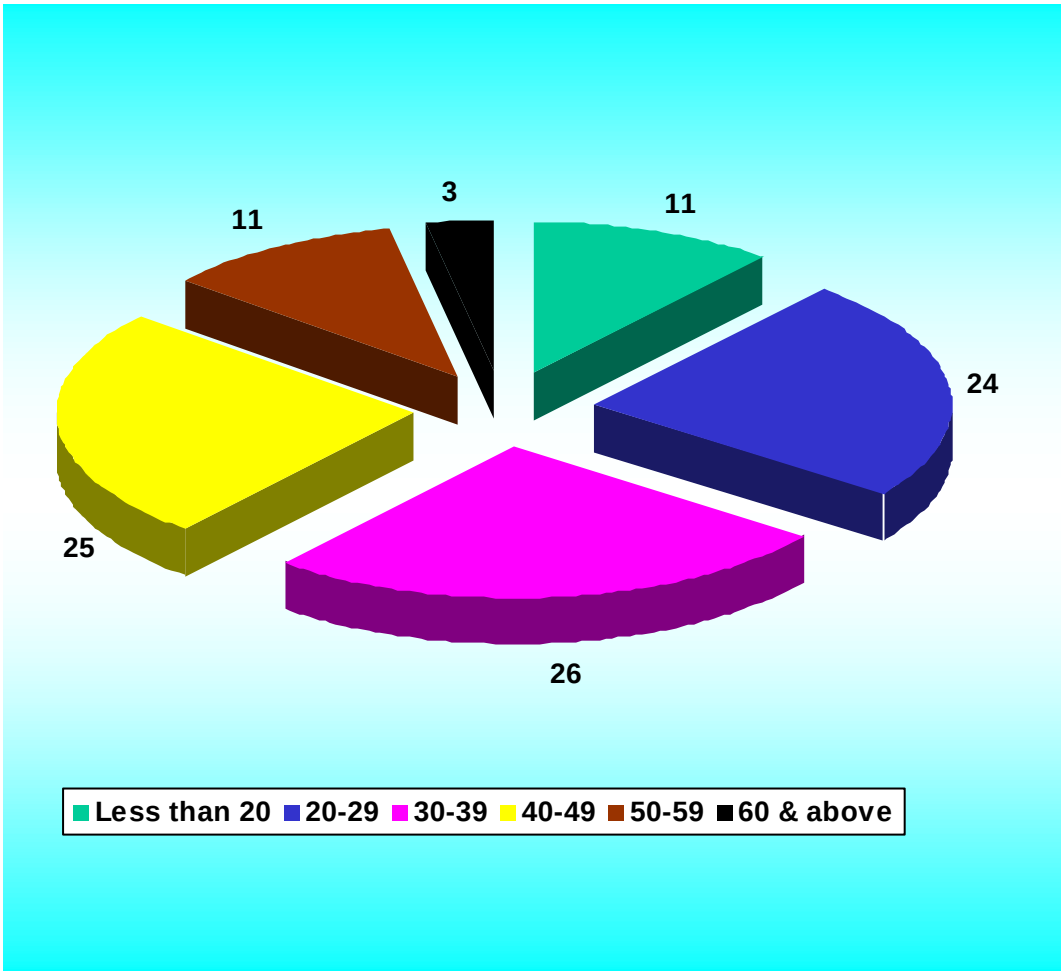
This study indicates the importance of myonecrosis in haemotoxic/ neurotoxic snake bite as a cause of snake failure. There are no extensive studies done correlating the myonecrosis in haemotoxic/ neurotoxic snake bite and renal failure.

Limitations of this study are 1) direct nephrotoxicity of the snake venom could not be excluded. 2) DIC as a cause of renal failure could not be excluded as DIC is commonly seen in rhabdomyolysis.

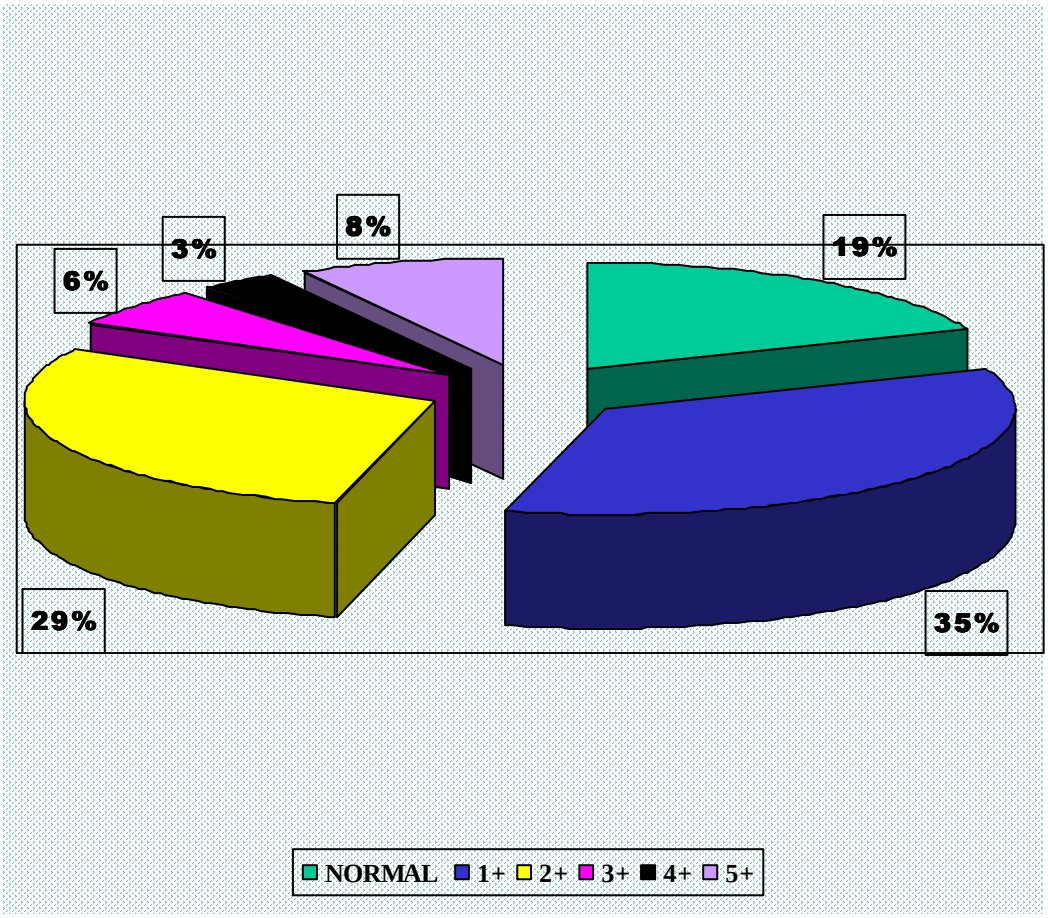
CONCLUSION

1) The incidence of myonecrosis in haemotoxic/ neurotoxic snake bite in our study is 81%. There is high incidence of myonecrosis in our study.
2) Viper and cobra bites are definitely associated with myonecrosis. Krait bite is not associated with myonecrosis. The degree of myonecrosis is highest in viper.
3) There is definite correlation between the severity of myonecrosis and ARF in snake bite.

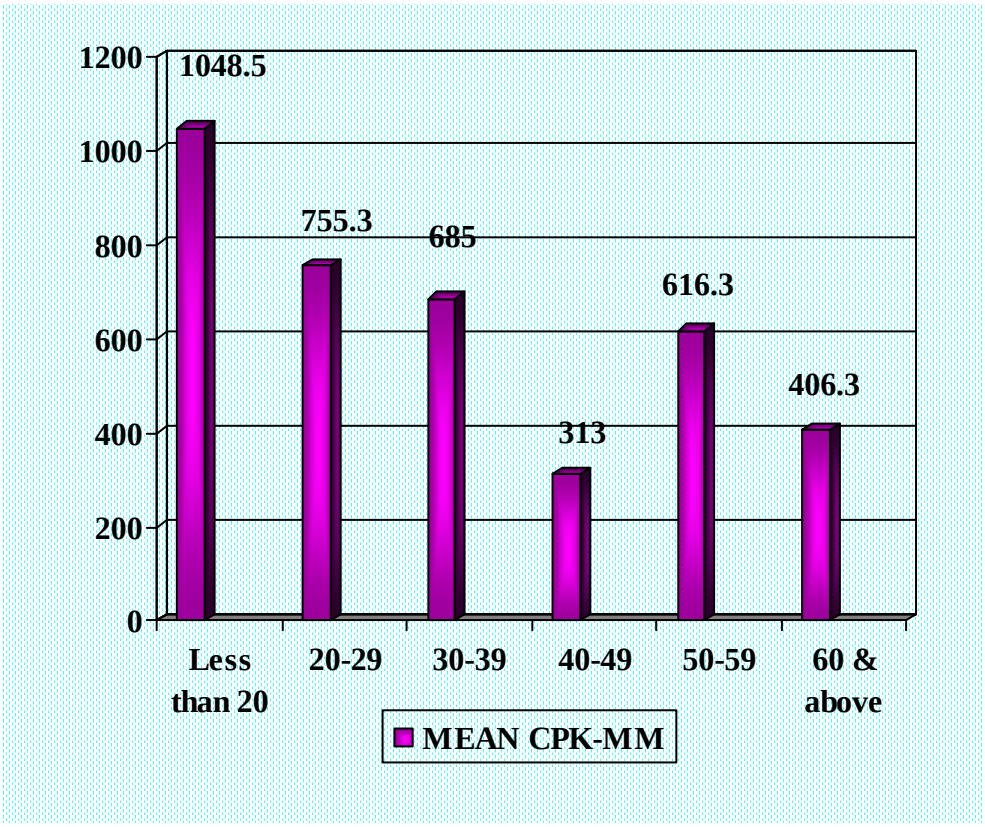
AGE DISTRIBUTION OF SNAKE BITE CASES



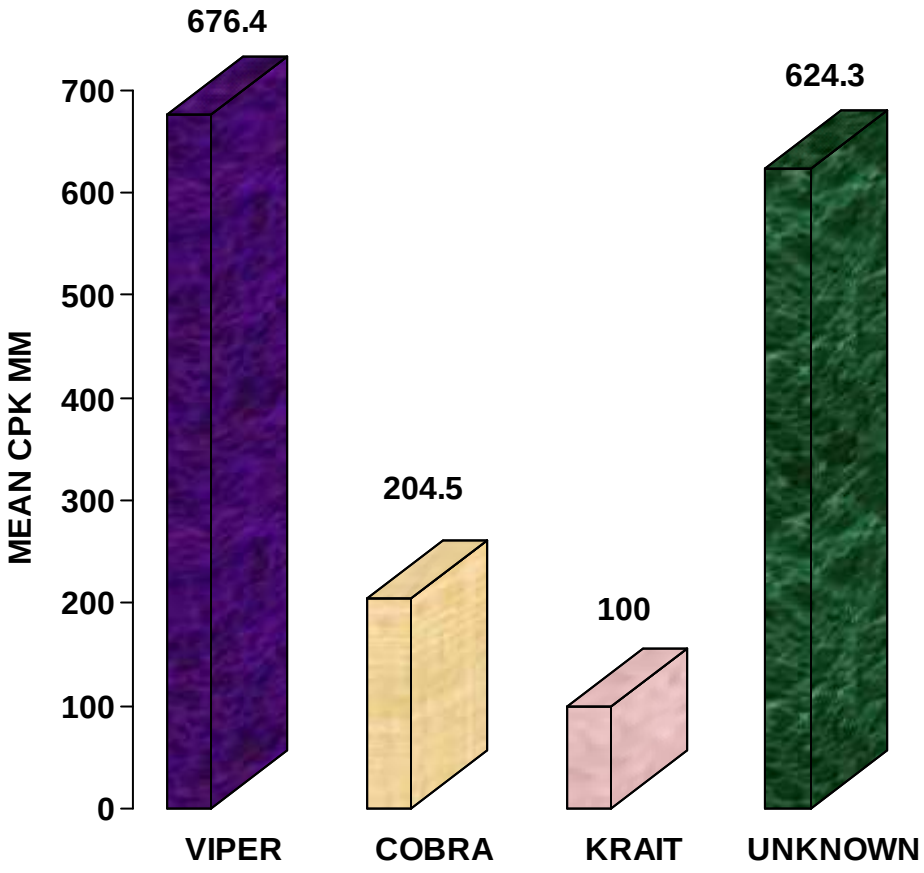
LEVEL OF CPK-MM IN SNAKE BITE PATIENTS



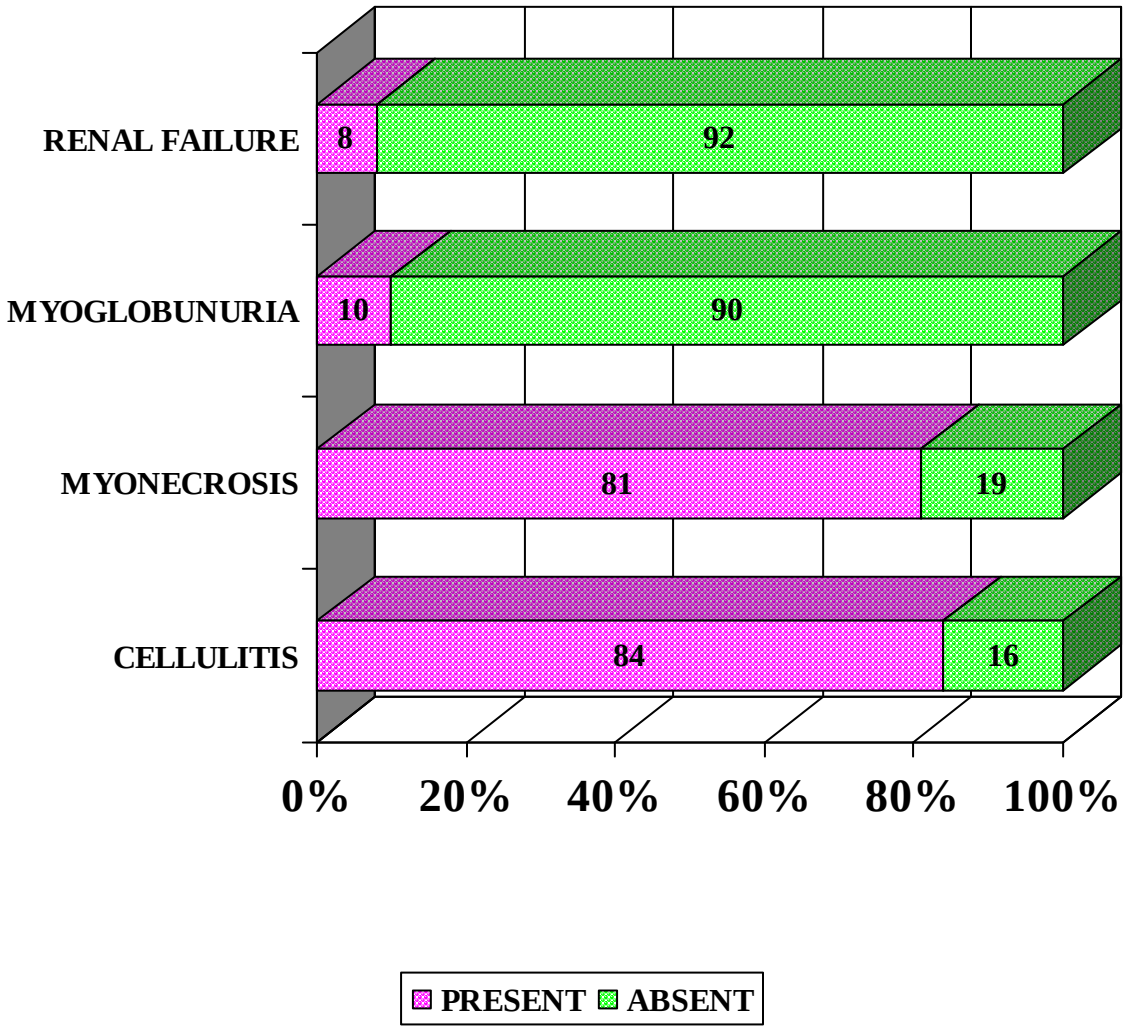
AGE DISTRIBUTION OF MYONECROSIS



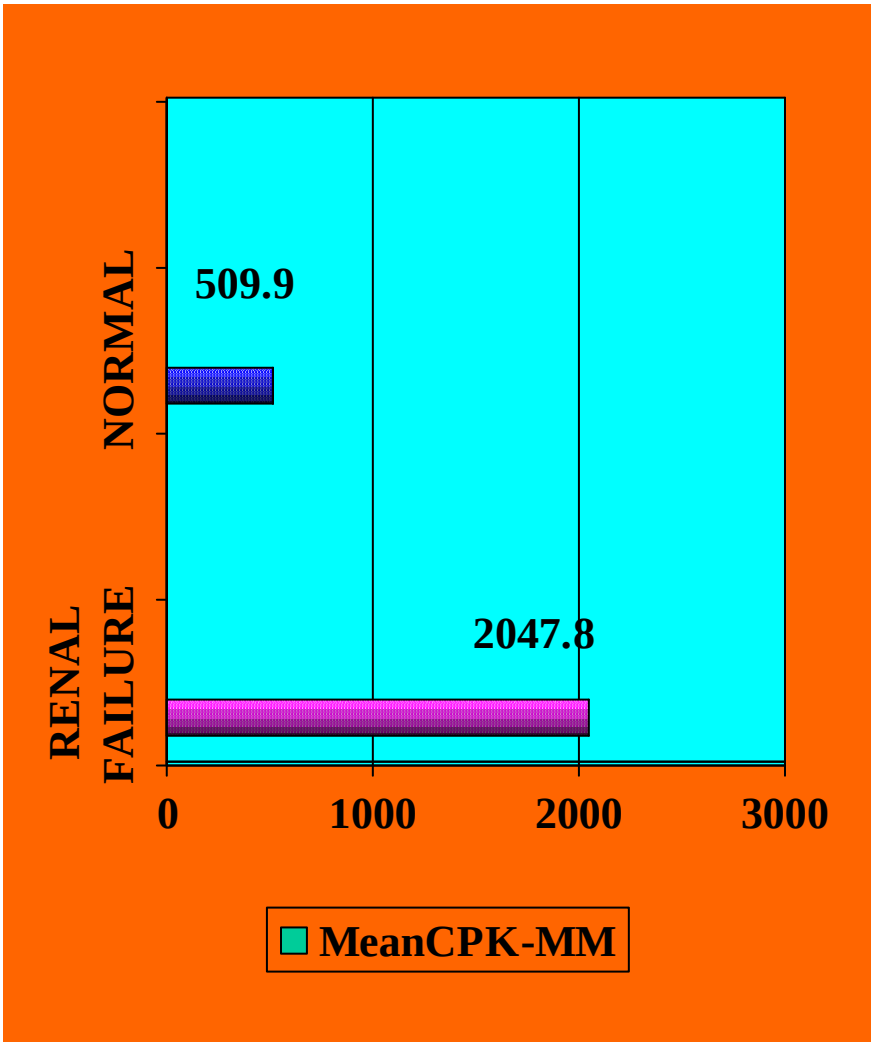
DEGREE OF MYONECROSIS IN VARIOUS TYPES OF SNAKE BITE



CORRELATION BETWEEN MYONECROSIS, MYOGLOBINURIA AND RENAL FAILURE



CORRELATION OF THE DEGREE OF MYONECROSIS WITH RENAL FAILURE



BANDED KRAIT

INDIAN COBRA

RUSSELL'S VIPER

CELLULITIS FOOT

BIBLIOGRAPHY

1) The Essentials of Forensic Medicine and Toxicology by Dr. K.S.Narayan Reddy– 22nd edition ; 462-467.
2) Parikh's textbook of Medical Jurisprudence, Forensic Medicine and Toxicology – 6th edition ; 9.40 – 9.49.
3) Modi's textbook of Medical Jurisprudence and Toxicology – 22nd edition ; 264-270.
4) API textbook of Medicine – 7th edition ; 1279-1282.
5) Diseases of the kidney by Robert W. Schrier and Carl W. Gottschalk – 6th edition ; 1273-1282.
6) Harrison's principles of Internal Medicine - 16th edition ; 2594-2595.
7) Chugh KS. Snake bite induced acute renal failure in India. Kidney Int 1989;35:891- 907.
8) Harding KA, Welch KR. Venomous Snakes of the World. Acute renal failure following snake bite. Am J Trop Med Hyg 1975;24:692-7.
9) Warrell DA. Snake venoms in science and clinical medicine. Russell's viper: Biology, venom and treatment of bites. Trans R Soc Trop Med Hyg 1989;83:732-40.
10) Chugh KS, Pal Y, Chakravarty RN, et al. Acute renal failure following poisonous snake bite. Am J Kidney Dis 1984;4:30-8.
11) Bicher HI, Roth M, Gitter S. Neurotoxic activity of Vipera palestinae venom. Depression of central autonomic vasoregulatory mechanisms. Med Pharmacol Exp. 1966;14: 349-59.

12) Peiris OA, Wimalaratne KD, Nimalasuriya A. Exchange transfusions in the treatment of Russell's viper bite. Postgrad Med J 1969;45:627-9.

13) Jeyarajah R. Russell's viper bite in Sri Lanka. A study of 22 cases. Am J Trop Med Hyg 1984;33:506-10.

14) Kahn MJ, Hemker HC. Studies on blood coagulation factor V. Changes of molecular weight accompanying activation of factor V by thrombin and the procoagulant protein of Russell's viper venom. Thromb Diath Haemorrh 1972;29:25-32.

15) Kisiel W, Hermodson MA, Davie EW. Factor X-activating enzyme from Russell's viper venom: isolation and characterization. Biochemistry 1976;15:4901-6.

16) Rosing J, Tans G. Structural and functional properties of snake venom prothrombin activators. Toxicon 1992;30:1515-27.

17) Ouyang C, Teng CM, Huang TF. Characterisation of snake venom components acting on blood coagulation and platelet function. Toxicon 1992;30:945-66.

18) Seedat YK, Reddy J, Edington DA. Acute renal failure due to proliferative nephritis from snakebite poisoning. Nephron 1974;13:455-63.

19) Reid HA. Myoglobinuria and sea-snake bite poisoning. Br Med J 1961;1:1284-9.

20) Myint Lwin, Warrell DA, Phillips RE, Tin NS, Tun Pe, Maung ML. Bites by Russell's viper (Vipera russelli siamensis) in Burma. Haemostatic, vascular, and renal disturbances and response to treatment. Lancet 1985;2:1259-64.

21) Than T, Hutton RA, Myint L, et al. Haemostatic disturbances in patients bitten by Russell's viper in Burma. Br J Haematol 1988;69:513-20.

22) Reid HA, Theakston RD. The management of snake bite. Bull WHO 1983;61:885- 95.

23) Juckett G, Hancox JG. Venomous snakebites in the United States: management review and update. Am Fam Physician 2002;65:1367-74.

24) Markland FSJr. Snake venoms. Drugs 1997;54(S3):1-10.

25) Markland FSJr. Inventory of alpha and beta-fibrinogenases from snake venom. Thromb Haemost 1991;65:438-43.

26) Sitprija V, Benyajati C, Boonpucknavig V. Further observations of renal insufficiency in snakebite. Nephron 1974; 13:396-403.

27) Lakier JB, Fritz VU. Consumptive coagulopathy caused by a bloomslang bite. S Afr Med J 1969;43:1052-5.

28) Chugh KS, Mohanthy D, Pal Y, Das KC, Ganguly NK, Chakravarty RN. Hemostatic abnormalities following Echis carinatus (saw scaled viper) envenomation in the rhesus monkey. Am J Trop Med Hyg 1981;30:1116-20.

29) Ang-Khin M. Histological and ultrastructural changes of the kidney in renal failure after viper envenomation. Toxicon 1978;16:71-5.

30) Schmidt ME, Abdelbaki YA, Tu AT. Nephrotoxic action of rattle snake and sea snake venom: an electron microscopic study. J Pathol 1976;118:75-81.

31) Greenwood BM, Warrell DA, Davidson NM, Ormerod LD, Reid HA. Immunodiagnosis of snakebite. Br Med J 1974;4:743-5.

32) Ratcliffe PJ, Pukrittayakamee S, Ledingham JG, Warrell DA. Direct nephrotoxicity of Russell's viper venom demonstrated in the isolated perfused rat kidney. Am J Trop Med Hyg 1989;40:312-9.

APPENDIX I – PROFORMA

SERUM CPK LEVELS IN SNAKE BITE AND CORRELATION WITH ACUTE RENAL FAILURE

NAME: **AGE:** **SEX:** **OCCUPATION:**

ADDRESS: **IP/OP NO:**

CLINICAL HISTORY:

TIME/DAY OF BITE **TYPE OF THE SNAKE**

PAIN/SWELLING AT THE SITE OF BITE

BLEEDING MANIFESTATIONS **NEUROTOXIC SYMPTOMS**

SEVERE MYALGIA

OLIGURIA/HEMATURIA/PEDAL EDEMA/FACIAL PUFFINESS

CLINICAL EXAMINATION:

GEN EXAMN:

VITAL DATA:

PULSE:

BP:

RR:

TEMP:

SYSTEMIC EXAMINATION:

CVS:

RS:

ABDOMEN:

CNS:

LOCAL EXAMINATION:

CELLULITIS

ACTIVE BLEED

FANG MARKS

DISTAL PULSES

GANGRENE

MUSCLE TENDERNESS

INVESTIGATIONS

Hb %

TC

DC

URINE ALBUMIN
SUGAR
DEPOSITS
MYOGLOBINURIA

PARAMETERS/DAY			
BLOOD SUGAR			
BLOOD UREA			
SERUM CREATININE			

SERUM CPK/DAY			
TOTAL			
MM			

CLOTTING TIME:

TIME/DAY				

ECG IN ALL LEADS:

APPENDIX II MASTER CHART

S.NO.	Name	Age	Sex	Type of Snake	Symptoms of renal failure	Cellulitis	CPK MM	CPK Grade	Myloglobin uria	Urea, Creatinine
1	Kirupanandham	13	Male	Viper	+	+	2102	5	+	Increase
2	Thangavelu	45	Male	Viper	-	+	372	1	-	N
3	Paramasamy	34	Male	Cobra	-	-	92	NORMAL	-	N
4	Malaiyappan	31	Male	Viper	-	+	340	1	-	N
5	Thangam	38	Male	Viper	-	+	628	2	-	N
6	Chinnaadaikkan	78	Male	Viper	-	+	456	1	-	N
7	Rameshbabu	17	Male	Viper	-	+	701	2	-	N
8	Ramasamy	55	Male	Viper	-	-	82	NORMAL	-	N
9	Azhagu	41	Male	Viper	-	+	400	1	-	N
10	Ramar	48	Male	Unknown	-	+	358	1	-	N
11	Ganesan	20	Male	Cobra	-	-	88	NORMAL	-	N
12	Karuppaiya	37	Male	Viper	-	+	456	1	-	N
13	Mayandi	42	Male	Viper	-	+	458	1	-	N
14	Muthu	23	Male	Unknown	-	+	401	1	-	N
15	Azhagu	25	Male	Viper	-	+	791	2	-	N
16	Ramu	55	Male	Viper	-	+	740	2	-	N
17	Perumayee	33	Female	Krait	-	-	96	NORMAL	-	N
18	Arumugam	50	Female	Viper	-	+	452	1	-	N
19	Balamurugan	14	Male	Viper	-	+	701	2	-	N
20	Venkatesh	21	Male	Unknown	-	-	109	NORMAL	-	N
21	Chitra	25	Female	Viper	-	+	1301	3	-	N
22	Valli	45	Female	Krait	-	-	96	NORMAL	-	N

S.NO.	Name	Age	Sex	Type of Snake	Symptoms of renal failure	Cellulitis	CPK MM	CPK Grade	Myloglobin uria	Urea, Creatinine
23	Alagarsamy	29	Male	Viper	-	+	842	2	-	N
24	Ganapathy	60	Male	Viper	-	+	654	2	-	N
25	Sivanandi	34	Male	Viper	-	+	832	2	-	N
26	Ramasamy	50	Male	Viper	-	+	581	2	-	N
27	Ayyanar	28	Male	Viper	+	+	2162	5	+	Increase
28	Srinivasan	13	Male	Unknown	-	-	112	NORMAL	-	N
29	Muthupillai	35	Female	Viper	+	+	2056	5	+	Increase
30	Mariappan	50	Male	Unknown	-	+	642	2	-	N
31	Muthu	37	Female	Viper	-	-	107	NORMAL	-	N
32	Ravi	40	Male	Viper	-	+	882	2	-	N
33	Murugesan	27	Male	Viper	-	+	668	2	-	N
34	Petchiammmal	40	Female	Viper	-	+	442	1	-	N
35	Murugaselvam	20	Male	unknown	+	+	2037	5	+	Increase
36	Mookammal	40	Female	viper	-	+	1172	3	-	N
37	Pitchai rajan	24	Male	Viper	-	+	248	1	-	N
38	Sakkarai	45	Male	Viper	-	-	89	NORMAL	-	N
39	Muniyandi	53	Male	Viper	-	+	1142	3	-	N
40	Andammal	20	Female	Viper	-	+	315	1	-	N
41	Vasanthi	45	Female	Unknown	-	-	108	NORMAL	-	N
42	Jeyaprakash	16	Male	Viper	-	+	358	1	-	N
43	Nagaraj	24	Male	Viper	-	-	91	NORMAL	-	N
44	Saravanabalan	30	Male	Cobra	-	+	399	1	-	N
45	Arunkumar	16	Male	Viper	-	+	761	2	-	N

S.NO.	Name	Age	Sex	Type of Snake	Symptoms of renal failure	Cellulitis	CPK MM	CPK Grade	Myloglobin uria	Urea, Creatinine
46	Manickam	42	Male	Unknown	-	+	170	1	-	N
47	Chellakannu	38	Male	Viper	-	+	1871	4	+	N
48	Sonaimuthu	25	Male	Viper	-	+	836	2	-	N
49	Kanthan	35	Male	Viper	-	+	674	2	-	N
50	Govindhan	40	Male	Viper	-	-	56	NORMAL	-	N
51	Ravichandran	40	Male	Viper	-	+	396	1	-	N
52	Rajendran	35	Male	Unknown	-	+	273	1	-	N
53	Paulpandy	32	Male	Viper	-	+	177	1	-	N
54	Kalimuthu	40	Male	Viper	-	-	76	NORMAL	-	N
55	Kamu	42	Male	Viper	-	+	442	1	-	N
56	Senthilkani	13	Female	Viper	+	+	2032	5	+	Increase
57	Amsam	39	Male	Viper	-	+	316	1	-	N
58	Mangaiyarkarasi	30	Female	Viper	-	+	227	1	-	N
59	Pounraj	45	Male	Unknown	-	-	91	NORMAL	-	N
60	Sekar	30	Male	Viper	-	+	1161	3	-	N
61	Ramesh	37	Male	Viper	-	+	1184	3	-	N
62	Perumal	25	Male	Unknown	+	+	1874	4	+	Increase
63	Muniyan	55	Male	viper	-	+	884	2	-	N
64	Ganesh	41	Male	Viper	-	+	232	1	-	N
65	Muthu	55	Male	Viper	-	+	171	1	-	N
66	Vairavan	20	Male	Viper	-	+	475	1	-	N
67	Thangaraj	43	Male	Viper	-	+	507	2	-	N
68	Murugan	30	Male	Viper	-	+	585	2	-	N

S.NO.	Name	Age	Sex	Type of Snake	Symptoms of renal failure	Cellulitis	CPK MM	CPK Grade	Myloglobin uria	Urea, Creatinine
69	Chinnammal	60	Female	Viper	-	-	109	NORMAL	-	N
70	Paulkanna	56	Male	Viper	-	+	547	2	-	N
71	Raju	27	Male	Viper	-	+	699	2	-	N
72	Chinnaiya	55	Male	Viper	-	+	788	2	-	N
73	Paramasivam	40	Male	Krait	-	-	108	NORMAL	-	N
74	Madhivanan	26	Male	Viper	+	+	2021	5	+	Increase
75	Kazhuvayee	39	Female	Viper	-	+	708	2	-	N
76	Lakshmanan	19	Male	Viper	-	+	696	2	-	N
77	Ochammal	55	Female	Unknown	-	+	750	2	-	N
78	Kannan	30	Male	Viper	-	+	436	1	-	N
79	Venkatesan	36	Male	Viper	+	+	2098	5	+	Increase
80	Lakshmi	33	Female	Viper	-	+	797	2	-	N
81	Ganga	13	Female	Viper	-	+	2031	5	+	N
82	Kannnan	39	Male	Viper	-	+	646	2	-	N
83	Rakku	35	Female	Unknown	-	+	890	2	-	N
84	Muthup andi	30	Female	Unknown	-	+	925	2	-	N
85	Muthu	20	Female	Viper	-	+	674	2	-	N
86	Chinnasamy	32	Male	Viper	-	+	135	NORMAL	-	N
87	Manimegalai	14	Female	Cobra	-	+	239	1	-	N
88	Vanitha	22	Female	Viper	-	+	1345	3	-	N
89	Muthupechi	27	Female	Viper	-	+	296	1	-	N
90	Kazhuvayee	40	Female	Viper	-	+	268	1	-	N
91	Selvi	23	Female	Viper	-	+	327	1	-	N

S.NO.	Name	Age	Sex	Type of Snake	Symptoms of renal failure	Cellulitis	CPK MM	CPK Grade	Myloglobin uria	Urea, Creatinine
92	Avudaiachi	48	Female	Viper	-	+	380	1	-	N
93	Alagammal	40	Female	Viper	-	+	234	1	-	N
94	Subramani	25	Male	Viper	-	+	130	NORMAL	-	N
95	Perumal	48	Male	Viper	-	+	142	1	-	N
96	Sureshkumar	27	Male	Viper	-	+	281	1	-	N
97	Suresh	41	Male	Viper	-	+	166	1	-	N
98	Mohammed Meeran	17	Male	Viper	-	+	1800	4	-	N
99	Thirumugam	44	Male	Viper	-	+	181	1	-	N
100	Sumathi	27	Female	Viper	-	+	115	NORMAL	-	N